

Efficient Niementowski synthesis of novel 1,3,10,12-tetra-substituted-8*H*-pyrido[2',3':4,5]pyrimido[6,1-*b*]quinazolin-8-ones

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Abstract

Novel 1,3,10,12-tetrasubstituted-8*H*-pyrido[2',3':4,5]pyrimido[6,1-*b*]quinazolin-8-ones were synthesised by a Niementowski reaction involving condensation of substituted anthranilic acids with a 5,7-disubstituted-3*H*-pyrido[2,3-*d*]pyrimidin-4-ones. Microwave irradiation in polyphosphoric acid media was used in order to improve reactions where classical or direct fusion method was limited. The synthesis of title compounds highlights a comparative study of the classical, microwave technique and direct fusion methods.

Keywords: Cyclization, fused pyrido[2,3-*d*]pyrimidine, microwave assisted synthesis, nitrogen heterocycles

Introduction

Quinazolines and condensed pyrimidines show a wide spectrum of biological activities and have been exhaustively reviewed. Pyrido [2,3-*d*] pyrimidines are considered to be bioisosteres of quinazolines. The concept of bioisosterism has been exploited by medicinal chemists as an approach to the drug design. This has led to the synthesis of various types of condensed pyrimidines, which show a wide range of biological activities. A rapid progress in the work on fused quinazolinones and pyridopyrimidines has given rise to a number of compounds exhibiting potent pharmacological actions like adenosine kinase inhibitory activity¹⁻³, EGFr and C-erbB-2 inhibitory activity⁴, antibacterials⁵, and phosphodiesterase 5 inhibitory activity⁶⁻⁹.

Examples of natural nitrogen heterocycles are Rutaecarpine which possesses intrinsic diuretic, uterotonic and hypertensive¹⁰, and Luotonine A3, which exhibits antitumor activity¹¹. These natural compounds contain a quinazolinone moiety fused with indolopyrido and pyrroloquinoline ring systems, respectively (Figure 1). In search of new fused heterocyclic compounds with potential pharmaceutical value and in association with our work on the application of microwaves in organic chemistry¹², we planned to prepare novel tetracyclic 1,3,10,12-tetrasubstituted-8*H*-pyrido[2',3':4,5]-pyrimido[6,1-*b*]quinazolin-8-ones **4**, from substituted

anthranilic acids **3** and pyrido[2,3-*d*]pyrimidines **2** which constitutes the Niementowski condensation²⁰.

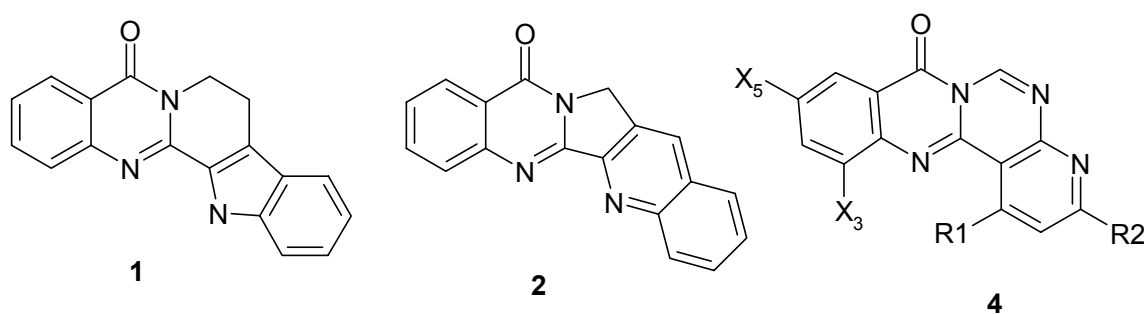


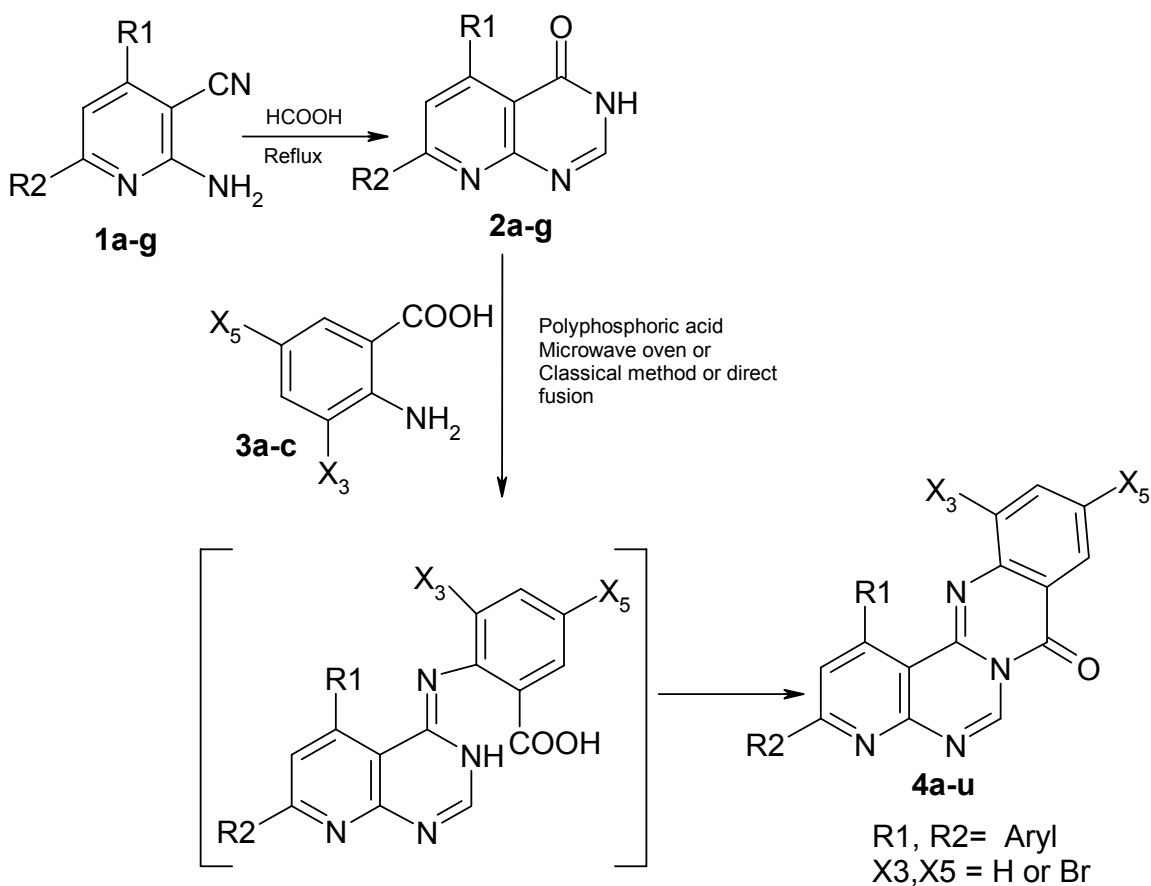
Figure 1

Microwave-assisted reactions are now well recognized and have gained popularity as indicated by the large number of papers currently published on this topic¹³⁻¹⁶. The beneficial effects of microwave irradiation are finding an increased role specially in process chemistry and in cases where usual methods require forcing conditions or prolonged reaction times. Microwaves have also shown an advantage when products may decompose under prolonged reaction conditions. The possibilities offered by microwave-assisted reactions are particularly attractive for multi-step synthesis¹⁷ and drug discovery process^{18, 19} where purification are highly desirable. In this paper the one-step synthesis of the novel pyrido[2',3':4,5]pyrimido[6,1-*b*]quinazolin-8-one ring was realized under microwave irradiation aimed at developing an original and environmentally friendly procedure.

To our knowledge, the 1,3,10,12-tetrasubstituted-8*H*-pyrido[2',3':4,5]-pyrimido[6,1-*b*]quinazolin-8-one skeleton has never been published yet. We suggested that generation of this novel ring may occur via a Niementowski reaction²⁰ between anthranilic acid and novel 5,7-disubstituted-3*H*-pyrido[2,3-*d*]pyrimidin-4-one.

Results and Discussion

The first step in this reaction involved the synthesis of pyrido[2,3-*d*]pyrimidin-4-one **2** which took place by reacting 2-amino-4,6-disubstitutednicotinonitriles **1** with formic acid. The second step of the route involves the reaction anthranilic acids **3** and pyrido[2,3-*d*]pyrimidines **2** to give the products **4** via the Niementowski condensation²⁰. The latter reaction is either carried out in microwave and by classical heating using polyphosphoric acid, or by the direct fusion method. It is assumed that formation of products **4** requires an intramolecular acyl substitution between the pyrimidine nitrogen and the carboxylic acid group of the intermediate carboxylic acid (Scheme 1).



Scheme 1

A comparative study of the three methods used for synthesizing compounds **4**, conventional heating (Method A), microwave heating (Method B) and direct fusion method (Method C) showed that the microwave method gave overall cleaner and higher yielding reactions (Table 1). To our knowledge, all compounds synthesised by this reaction are novel.

Table 1. Physical data of compound 4a-u

Com pd	Substitution				Reaction time		Yield (%)			M.p. (°C)
					(min)					
	R ¹	R ²	X ³	X ⁵	Method		Method			
				A	B	A	B	C		
4a	2-furfuryl	4-tolyl	H	H	180	05	70	85	20	120-122
4b	4-methoxy- phenyl	phenyl	H	H	160	04	75	90	25	106-108
4c	Phenyl	4-chloro- phenyl	H	H	180	07	65	85	30	96-98
4d	3-nitro- phenyl	4-methoxy- phenyl	H	H	180	07	68	90	25	138-140
4e	4-nitro- phenyl	4-nitro- phenyl	H	H	190	08	75	95	30	160-162
4f	4-tolyl	Phenyl	H	H	190	08	70	90	20	110-112
4g	4-chloro- phenyl	4-tolyl	H	H	180	07	62	80	20	120-122
4h	2-furfuryl	4-tolyl	Br	Br	210	09	60	85	-	130-132
4i	4-methoxy- phenyl	phenyl	Br	Br	210	10	65	80	20	156-158
4j	Phenyl	4-chloro- phenyl	Br	Br	210	10	68	85	30	198-200
4k	3-nitro- phenyl	4-methoxy- phenyl	Br	Br	210	10	60	80	35	108-110
4l	4-nitro- phenyl	4-nitro- phenyl	Br	Br	190	08	65	80	-	128-130
4m	4-tolyl	Phenyl	Br	Br	210	10	68	78	20	116-118
4n	4-chloro- phenyl	4-tolyl	Br	Br	190	09	70	85	25	178-180
4o	2-furfuryl	4-tolyl	H	Br	190	08	70	80	20	138-140
4p	4-methoxy- phenyl	phenyl	H	Br	190	08	72	85	20	100-102
4q	Phenyl	4-chloro- phenyl	H	Br	190	09	70	80	-	220-222
4r	3-nitro- phenyl	4-methoxy- phenyl	H	Br	210	09	68	80	-	198-200
4s	4-nitro- phenyl	4-nitro- phenyl	H	Br	210	10	60	75	-	234-236
4t	4-tolyl	Phenyl	H	Br	210	10	70	90	20	120-122
4u	4-chloro- phenyl	4-tolyl	H	Br	210	10	75	90	20	150-152

The IR (KBr) spectra of **4** showed characteristic C=O stretching vibrations in the region 1785-1650 cm^{-1} . The C=C and C=N ring stretching vibrations appeared in the area around 1620 and 1570-1520 cm^{-1} . The IR bands due to NH and COOH vibrations were not present in any of the spectrum of the compound **4** which ruled out the possibility of any remaining uncyclised material.

The direct cyclization to compounds **4** is also supported by ^1H NMR spectral data of these compounds since no resonance due to the NH or OH protons appeared in any of the spectra.

Conclusions

In conclusion, we described the rapid and efficient synthesis to novel tetracyclic 1,3,10,12-tetrasubstituted-8*H*-pyrido[2',3':4,5]pyrimido[6,1-*b*]quinazolin-8-ones **4**, from substituted anthranilic acids **3** and pyrido[2,3-*d*]pyrimidines **2**. The best method used is microwave irradiation in the presence of polyphosphoric acid where reaction is complete within 10 min in contrast to classical heating which requires 3.5 h. The benefits of microwave irradiation are noticeable since high temperatures, lengthy and tedious conditions are required otherwise. The synthesized Pyrido[2',3':4,5]pyrimido[6,1-*b*]-quinazolin-8-ones are structurally related to previously studied terrestrial alkaloids, Rutaecarpine and Luotonine A and therefore phosphodiesterase inhibitory activity of various analogues of these compounds is being studied and will be described later.

Experimental Section

General Procedures. The microwave assisted synthesis were performed in scientific microwave oven RAGA's microwave oven. Melting points were determined in open capillaries using a Thermonik C-PMB-2 precision melting point and boiling point apparatus, (Mumbai, India) and are uncorrected. The purity of the compound was routinely checked by TLC using silica gel-G and the spots were exposed in iodine vapour. IR spectra were recorded using KBr pellets on a Shimadzu 1600 Spectrophotometer from Shimadzu International Incorporation, (Vmax cm^{-1}), ^1H NMR spectra on Bruker Avance 400 Spectrometer (Bruker AG, Fallanden, Switzerland) at 400 MHz using TMS as internal standard (Solvent CDCl_3 and chemical shift in δ ppm) and mass spectra (EI-MS) were recorded on a Jeol SX-102 spectrometer (Jeol Ltd. Tokyo, Japan). Elemental analyses were carried out at Heraeus Carlo Erba 1180 CHN analyzer (from Heraeus Instrument GmbH, Hanau, Germany). All the chemicals were purchased from Aldrich Company Ltd. Dorset (UK).

Synthesis of 2-amino-4,6-disubstituted-nicotinonitriles(1a-g). These compounds were synthesized from substituted chalcones using known procedure ²¹. The product **1a-g** on recrystallization from ethanol was obtained in pure form.

Synthesis of 3H-pyrido[2,3-d]pyrimidin-4-ones (2a-g). The appropriate compound **1a-g** (0.01 mol) in formic acid (20 mL, 85%) was refluxed for 3 h, cooled, poured onto ice-water to give a precipitate, which was filtered off, dried and recrystallised from ethanol to afford title compounds **2a-g**, respectively.

Synthesis of anthranilic acids (3a-c). The monobromo and dibromo anthranilic acids **3a-c** were synthesized according to the reported method²².

Synthesis of 8H-pyrido[2',3':4,5]pyrimido[6,1-b]quinazolin-8-ones (4a-u): General procedures

Method A (classical)

A mixture of the appropriate compound **2a-g** (0.61 mmole) and anthranilic acid **3a-c** (3.4 mmole) in polyphosphoric acid (5 ml) was stirred and heated at 160°C for 4 hours. The reaction mixture was cooled, slowly added to ice-water mixture and neutralized with aqueous ammonia after which a solid precipitated. The solid was filtered, washed with water, dried and recrystallised from ethanol to yield the corresponding title compound **4a-u**.

Method B (microwave)

A mixture of the appropriate compound **2a-g** (0.61 mmole) and anthranilic acid **3a-c** (3.4 mmole) in polyphosphoric acid (5ml) was introduced in Pyrex tube. The Pyrex tube was irradiated for 10 min (power output 140W). The reaction tube was cooled, slowly added to ice-water mixture and neutralized with aqueous ammonia when a solid precipitated. The solid was filtered, washed with water, dried and recrystallised from ethanol to yield the corresponding title compound **4a-u**.

Method C (direct fusion method)

In a round bottom flask, a mixture of the appropriate compound **2a-g** (0.61 mmole) and anthranilic acid **3a-c** (3.4 mmole) were ground thoroughly and the mixture was heated above its melting point (+5°C). The reaction mixture was kept in molten state for 5-10 minutes and then was cooled gradually. The residue obtained on cooling was triturated with petroleum ether, filter and recrystallised from ethanol to yield the corresponding title compound **4a-u**.

1-(2-Furyl)-3-(4-methylphenyl)-8H-pyrido[2',3':4,5]pyrimido[6,1-b]quinazolin-8-one (4a).

IR (KBr) ν_{\max} : 1757 (C=O), 1608 (C=N) cm^{-1} ; ¹H-NMR (400 MHz, CDCl₃) δ (ppm): 2.48 (s, 3H, CH₃), 6.62-8.89 (m, 13H, Ar-H); ¹³C-NMR (75 MHz, CDCl₃) δ (ppm): 21.3, 107.6, 112, 116.9, 120.3, 120.8, 123.3, 123.3, 126.6, 126.7, 127.3, 129.5, 129.5, 130.3, 133.4, 136, 142.9, 143.6, 114.5, 148.7, 154, 155.9, 157.8, 163, 170.6; *m/z* (EI): 404.13 (25%); Anal. calcd for C₂₅H₁₆N₄O₂: C, 74.25; H, 3.99; N, 13.85%. Found: C, 74.54; H, 3.78; N, 13.70%.

1-(4-Methoxy-phenyl)-3-phenyl-8H-pyrido[2',3':4,5]pyrimido[6,1-b]quinazolin-8-one (4b).

IR (KBr) ν_{\max} : 1751 (C=O), 1685 (C=N) cm^{-1} ; ¹H-NMR (400 MHz, CDCl₃, δ in ppm) 3.84

(s,3H, OCH₃), 6.89-8.93 (m, 15H Ar-H) , ¹³C-NMR (CDCl₃, 75 MHz, δ in ppm) 55.8, 114.8, 114.8, 116.3, 119.7, 120.8, 126.6, 126.7, 127.3, 127.3, 127.6, 127.6, 129.2, 129.2, 129.6, 129.6, 133.2, 133.4, 139, 144.5, 148.5, 148.6, 155.9, 157.7, 161.1, 163, 170.6 ; *m/z* (EI): 430.14 (30%); Anal. calcd for C₂₇H₁₈N₄O₂: C, 75.34; H, 4.21; N, 13.02%. Found: C, 75.48; H, 4.12; N, 13.32%

3-(4-Chloro-phenyl)-1-phenyl-8*H*-pyrido[2',3':4,5]pyrimido[6,1-*b*]quinazolin-8-one (4c). IR (KBr) *v*_{max}:1685 (C=O), 1608 (C=N) cm⁻¹; ¹H-NMR (400 MHz, CDCl₃, δ in ppm) 7.01-8.49 (m, 15H Ar-H) , ¹³C-NMR (CDCl₃, 75 MHz, δ in ppm) 116.3, 119.7, 120.8, 126.6, 126.7, 127.3, 127.4, 127.4, 129, 129, 129.2, 129.2, 129.2, 129.3, 129.3, 132.9, 133.4, 137.1, 140.9, 144.5, 148.5, 148.6, 155.9, 157.7, 163, 170.6 ; *m/z* (EI): 434.09 (20%); Anal. calcd for C₂₆H₁₅ClN₄O: C,71.81; H, 3.48; N, 12.88%. Found: C, 71.98; H, 3.37; N, 12.94%.

3-(4-Methoxy-phenyl)-1-(3-nitro-phenyl)-8*H*-pyrido[2',3':4,5]pyrimido[6,1-*b*]quinazolin-8-one (4d). IR (KBr) *v*_{max}:1757 (C=O), 1676 (C=N) cm⁻¹; ¹H-NMR (400 MHz, CDCl₃, δ in ppm) 3.84 (s, 3H, OCH₃), 7.87-8.85 (m, 14H Ar-H) , ¹³C-NMR (CDCl₃, 75 MHz, δ in ppm) 55.8, 114.8, 114.8, 116.3, 119.7, 119.9, 120.8, 121.6, 126.6, 126.7, 127.3, 128.6, 128.6, 130, 131.3, 133.4, 134.4, 138.8, 144.5, 148.5, 148.6, 155.9, 157.7, 159.2, 163, 166.4, 170.6 ; *m/z* (EI): 476.14 (20%); Anal. calcd for C₂₇H₁₈N₅O₄: C, 68.06; H, 3.81; N, 14.70%. Found: C, 68.23; H, 3.72; N, 14.82%.

1,3-Bis-(4-nitro-phenyl)-8*H*-pyrido[2',3':4,5]pyrimido[6,1-*b*]quinazolin-8-one (4e). IR (KBr) *v*_{max}: 1750 (C=O), 1610 (C=N) cm⁻¹; ¹H-NMR (400 MHz, CDCl₃, δ in ppm) 7.01-8.69 (m, 14H Ar-H) , ¹³C-NMR (CDCl₃, 75 MHz, δ in ppm) 116.3, 119.7, 120.8, 124.4, 124.4, 124.4, 124.4, 126.3, 126.3, 126.6, 126.7, 127.3, 128.3, 128.3, 133.4, 144.5, 145.1, 146.5, 147, 148.4, 148.5, 148.6, 155.9, 157.7, 163, 170.6 ; *m/z* (EI): 490.10 (21%);Anal. calcd for C₂₆H₁₄N₆O₅: C, 63.67; H, 2.88; N, 17.14%. Found: C, 63.52; H, 2.52; N 17.28%.

1-Phenyl-3-(4-tolyl)-8*H*-pyrido[2',3':4,5]pyrimido[6,1-*b*]quinazolin-8-one (4f). IR (KBr) *v*_{max}: 1700 (C=O), 1608 (C=N) cm⁻¹; ¹H-NMR (400 MHz, CDCl₃, δ in ppm) 2.48 ((s,3H, CH₃)), 6.7-8.83 (m, 15H) , ¹³C NMR (CDCl₃, 75 MHz, δ in ppm) 21.3, 116.3, 119.7, 120.8, 123.3, 123.3, 126.6, 126.7, 127.3, 127.4, 127.4, 129.2, 129.2, 129.2, 129.5, 129.5, 130.3, 133.4, 136, 140.9, 144.5, 148.5, 148.6, 155.9, 157.7, 163, 170.6 ; *m/z* (EI): 414.15 (24%); Anal. calcd for C₂₇H₁₈N₄O : C, 78.24; H, 4.38; N, 13.52%. Found: C, 78.32; H, 4.22; N, 13.48%.

1-(4-Chloro-phenyl)-3-(4-tolyl)-8*H*-pyrido[2',3':4,5]pyrimido[6,1-*b*]quinazolin-8-one (4g). IR (KBr) *v*_{max}: 1789 (C=O), 1667 (C=N) cm⁻¹; ¹H-NMR (400 MHz, CDCl₃, δ in ppm) 2.48 ((s,3H, CH₃), 6.58-8.43 (m, 14H) , ¹³C NMR (CDCl₃, 75 MHz, δ in ppm) 21.3, 116.3, 119.7, 120.8, 123.3, 123.3, 126.6, 126.7, 127.3, 128.8, 128.8, 129.3, 129.3, 129.5, 129.5, 130.3, 133.4, 134.8, 136, 139, 144.5, 148.5, 148.6, 155.9, 157.7, 163, 170.6 ; *m/z* (EI): 448.11 (19%); Anal. calcd for C₂₇H₁₇ClN₄O: C, 72.24; H, 3.82; N, 12.48%. Found: C, 72.38; H, 3.68; N, 12.29%.

9,11-Dibromo-1-(2-furyl)-3-(4-tolyl)-8*H*-pyrido[2',3':4,5]pyrimido[6,1-*b*]quinazolin-8-one (4h). IR (KBr) *v*_{max}: 1766 (C=O), 1608 (C=N) cm⁻¹; ¹H-NMR (400 MHz, CDCl₃, δ in ppm) 2.33 (s,3H, CH₃), 6.98-8.45 (m, 11H Ar-H) , ¹³C NMR (CDCl₃, 75 MHz, δ in ppm) 21.3, 107.1, 112, 113.2, 116.9, 120.3, 122, 123.3, 123.3, 125.2, 129.5, 129.5, 130.3, 131.3, 136, 139.4, 142.9,

143.6, 148.7, 150.1, 154, 155.9, 157.8, 163, 170.6 ; m/z (EI): 561.95 (25%); Anal. calcd for $C_{25}H_{14}Br_2N_4O_2$: C, 53.41; H, 2.51; N, 9.97%. Found: C, 53.22; H, 2.78; N, 9.62%.

9,11-Dibromo-1-(4-methoxy-phenyl)-3-phenyl-8H-pyrido[2',3':4,5]pyrimido[6,1-b]quinazolin-8-one (4i). IR (KBr) ν_{max} : 1710 (C=O), 1600 (C=N) cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$, δ in ppm) 3.84 (s, 3H, OCH₃), 6.98-8.76 (m, 13H Ar-H) , ^{13}C -NMR ($CDCl_3$, 75 MHz, δ in ppm) 55.8, 113.2, 114.8, 114.8, 116.3, 119.7, 122, 125.2, 127.2, 127.3, 127.6, 127.6, 129.2, 129.2, 129.6, 129.6, 131.3, 133.2, 139, 139.4, 148.5, 148.6, 150.1, 155.9, 157.7, 161.1, 163, 170.6 ; m/z (EI): 587.96 (19%); Anal. calcd for $C_{27}H_{16}Br_2N_4O_2$: C, 55.13; H, 2.74; N, 9.52%. Found: C, 55.29; H, 2.64; N 9.80%.

9,11-Dibromo-3-(4-chloro-phenyl)-1-phenyl-8H-pyrido[2',3':4,5]pyrimido[6,1-b]quinazolin-8-one (4j). IR (KBr) ν_{max} : 1701 (C=O), 1610 (C=N) cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$, δ in ppm) 7.43-8.78 (m, 13H Ar-H) , ^{13}C NMR ($CDCl_3$, 75 MHz, δ in ppm) 113.2, 116.3, 119.7, 122, 125.2, 127.4, 127.4, 129, 129, 129.2, 129.2, 129.2, 129.3, 129.3, 131.3, 132.9, 137.1, 139.4, 140.9, 148.5, 148.6, 150.1, 155.9, 157.7, 163, 170.6 ; m/z (EI): 591.91 (20%); Anal. calcd for $C_{26}H_{13}Br_2ClN_4O$: C, 52.69; H, 2.21; N, 9.45%. Found: C, 52.78; H, 2.48; N, 9.28%.

9,11-Dibromo-3-(4-methoxy-phenyl)-1-(3-nitro-phenyl)-8H-pyrido[2',3':4,5] pyrimido [6,1-b]quinazolin-8-one (4k). IR (KBr) ν_{max} : 1685 (C=O), 1608 (C=N) cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$, δ in ppm) 3.48 (s,3H, OCH₃), 6.4-8.38 (m, 12H Ar-H) , ^{13}C NMR ($CDCl_3$, 75 MHz, δ in ppm) 55.8, 113.2, 114.8, 114.8, 116.3, 119.7, 122, 122.7, 124.4, 125.2, 128.6, 128.6, 130.1, 131.3, 1.31.3, 133.5, 138.9, 139.4, 148.4, 148.5, 148.6, 150.1, 155.9, 157.7, 159.2, 163, 170.6 ; m/z (EI): 632.95 (27%); Anal. calcd for : $C_{27}H_{15}Br_2N_5O_4$ C, 51.21; H, 2.39; N, 11.06%. Found: C, 51.48; H, 2.48; N, 11.21%.

9,11-Dibromo-1,3-bis-(4-nitro-phenyl)-8H-pyrido[2',3':4,5]pyrimido[6,1-b]quinazolin-8-one (4l). IR (KBr) ν_{max} : 1701 (C=O), 1612 (C=N) cm^{-1} ; 1HNMR (400 MHz, $CDCl_3$, δ in ppm) 7.48-8.90 (m, 12H Ar-H) , ^{13}C NMR ($CDCl_3$, 75 MHz, δ in ppm) 113.2, 116.3, 119.7, 122, 124.4, 124.4, 124.4, 124.4, 125.2, 126.3, 126.3, 128.3, 128.3, 131.3, 139.4, 145.1, 146.5, 147, 148.4, 148.5, 148.6, 150.1, 155.9, 157.7, 163, 170.6 ; m/z (EI): 647.92 (19%); Anal. calcd for $C_{26}H_{12}Br_2N_6O_5$: C, 48.17; H, 1.87; N, 12.96%. Found: C, 48.37; H, 1.94; N, 12.82%.

9,11-Dibromo-1-phenyl-3-(4-tolyl)-8H-pyrido[2',3':4,5]pyrimido[6,1-b]quinazolin-8-one (4m). IR (KBr) ν_{max} : 1762 (C=O), 1610 (C=N) cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$, δ in ppm) 2.43 (s,3H, CH₃), 6.62-8.47 (m, 13 H Ar-H) , ^{13}C NMR ($CDCl_3$, 75 MHz, δ in ppm) 21.3, 113.2, 116.3, 119.7, 122, 123.3, 123.3, 125.2, 127.4, 127.4, 129.2, 129.2, 129.2, 129.5, 129.5, 130.3, 131.3, 136, 139.4, 140.9, 148.5, 148.6, 150.1, 155.9, 157.7, 163, 170.6 ; m/z (EI): 571.97 (21%); Anal. calcd for $C_{27}H_{16}Br_2N_4O$: C, 56.67; H, 2.82; N, 9.79%. Found: C, 56.37; H, 2.73; N 9.59%.

9,11-Dibromo-1-(4-chloro-phenyl)-3-(4-tolyl)-8H-pyrido[2',3':4,5]pyrimido[6,1-b]quinazolin-8-one (4n). IR (KBr) ν_{max} : 1712 (C=O), 1602 (C=N) cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$, δ in ppm) 2.41 (s,3H, CH₃), 7.18-8.52 (m, 15H Ar-H) , ^{13}C NMR ($CDCl_3$, 75 MHz, δ in ppm) 21.3, 113.2, 116.3, 119.7, 122, 123.3, 123.3, 125.2, 128.8, 128.8, 129.3, 129.3, 129.5, 129.5, 130.3, 131.3, 134.8, 136, 139, 139.4, 148.5, 148.6, 150.1, 155.9, 157.7, 163, 170.6 ; m/z (EI):

605.93 (17%); Anal. calcd for $C_{27}H_{15}Br_2ClN_4O$: C, 53.45; H, 2.49; N, 9.23%. Found: C, 53.83; H, 2.73; N, 9.13%.

9-Bromo-1-(2-furyl)-3-(4-tolyl)-8H-pyrido[2',3':4,5]pyrimido[6,1-b]quinazolin-8-one (4o). IR (KBr) ν_{max} : 1708 C=O stretching, 1608 C=N stretching; 1H NMR (400 MHz, $CDCl_3$, δ in ppm) 2.38 (s, 3H, CH₃), 6.98-8.72 (m, 12H Ar-H), ^{13}C NMR ($CDCl_3$, 75 MHz, δ in ppm) 21.3, 107.1, 112, 116.9, 120.3, 121.7, 123, 123.3, 123.3, 124.6, 129.5, 129.5, 130.3, 132.3, 136, 136.3, 142.9, 143.5, 143.6, 148.7, 154, 155.9, 157.8, 163, 170.6; m/z (EI): 484.04 (22%); Anal. calcd for $C_{25}H_{15}BrN_4O_2$: C, 62.13; H, 3.13; N, 11.59%. Found: C, 62.31; H, 3.28; N, 11.72%.

9-Bromo-1-(4-methoxy-phenyl)-3-phenyl-8H-pyrido[2',3':4,5]pyrimido[6,1-b]quinazolin-8-one (4p). IR (KBr) ν_{max} : 1757 (C=O), 1608 (C=N) cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$, δ in ppm) 3.88 (s, 3H, OCH₃), 6.63-8.83 (m, 14H Ar-H), ^{13}C NMR ($CDCl_3$, 75 MHz, δ in ppm) 55.8, 114.8, 114.8, 116.3, 119.7, 121.7, 123, 124.6, 127.3, 127.6, 127.6, 129.2, 129.2, 129.6, 129.6, 132.3, 133.2, 136.3, 139, 143.5, 148.5, 148.6, 155.9, 157.7, 161.1, 163, 170; m/z (EI): 508.05 (19%); Anal. calcd for $C_{27}H_{17}BrN_4O_2$: C, 63.67; H, 3.36; N, 11.00%. Found: C, 63.90; H, 3.12; N, 11.29%.

9-Bromo-3-(4-chloro-phenyl)-1-phenyl-8H-pyrido[2',3':4,5]pyrimido[6,1-b]quinazolin-8-one (4q). IR (KBr) ν_{max} : 1768 (C=O), 1682 (C=N) cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$, δ in ppm) 7.03-8.69 (m, 14H Ar-H), ^{13}C NMR ($CDCl_3$, 75 MHz, δ in ppm) 116.3, 119.7, 121.7, 123, 124.6, 127.4, 127.4, 129, 129, 129.2, 129.2, 129.2, 129.3, 129.3, 132.3, 132.9, 136.3, 137.1, 140.9, 143.5, 148.5, 148.6, 155.9, 157.7, 163, 170.6; m/z (EI): 514.00 (27%); Anal. calcd for $C_{26}H_{14}BrClN_4O$: C, 60.78; H, 2.75; N, 10.90%. Found: C, 60.42; H, 2.92; N, 10.67%.

9-Bromo-3-(4-methoxy-phenyl)-1-(3-nitro-phenyl)-8H-pyrido[2',3':4,5]pyrimido [6,1-b]quinazolin-8-one (4r). IR (KBr) ν_{max} : 1710 (C=O), 1608 (C=N) cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$, δ in ppm) 3.78 (s, 3H, OCH₃), 6.98-8.78 (m, 13H Ar-H), ^{13}C NMR ($CDCl_3$, 75 MHz, δ in ppm) 55.8, 114.8, 114.8, 116.3, 119.7, 121.7, 122.7, 124.4, 124.6, 128.6, 128.6, 130.1, 131.3, 132.3, 133.5, 136.3, 138.9, 143.5, 148.4, 148.5, 148.6, 155.9, 157.7, 159.2, 163, 170.6; m/z (EI): 553.04 (17%); Anal. calcd for $C_{27}H_{16}BrN_5O_4$: C, 58.50; H, 2.91; N, 12.63%. Found: C, 58.72; H, 2.98; N, 12.51%.

9-Bromo-1,3-bis-(4-nitro-phenyl)-8H-pyrido[2',3':4,5]pyrimido[6,1-b]quinazolin-8-one (4s). IR (KBr) ν_{max} : 1708 (C=O), 1610 (C=N) cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$, δ in ppm) 7.28-8.79 (m, 13H Ar-H), ^{13}C -NMR ($CDCl_3$, 75 MHz, δ in ppm) 116.3, 119.7, 121.7, 123, 124.4, 124.4, 124.4, 124.4, 124.6, 126.3, 126.3, 128.3, 128.3, 132.3, 136.3, 143.5, 145.1, 146.5, 147, 148.4, 148.5, 148.6, 155.9, 157.7, 163, 170.6; m/z (EI): 568.01 (20%); Anal. calcd for $C_{26}H_{13}BrN_6O_5$: C, 54.85; H, 2.30; N, 14.76%. Found: C, 54.81; H, 2.19; N, 14.23%.

9-Bromo-1-phenyl-3-(4-tolyl)-8H-pyrido[2',3':4,5]pyrimido[6,1-b]quinazolin-8-one (4t). IR (KBr) ν_{max} : 1685 (C=O), 1595 (C=N) cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$, δ in ppm) 2.43 (s, 3H, CH₃), 6.5-8.43 (m, 14H Ar-H), ^{13}C -NMR ($CDCl_3$, 75 MHz, δ in ppm) 21.3, 116.3, 119.7, 121.7, 123, 123.3, 123.3, 124.6, 127.4, 127.4, 129.2, 129.2, 129.2, 129.5, 129.5, 130.3, 132.3, 136, 136.3, 140.9, 143.5, 148.5, 148.6, 155.9, 157.7, 163, 170.6; m/z (EI): 492.06 (21%); Anal. calcd for $C_{27}H_{17}BrN_4O$: C, 65.73; H, 3.47; N, 11.36%. Found: C, 65.91; H, 3.71; N, 11.68%.

9-Bromo-1-(4-chloro-phenyl)-3-(4-tolyl)-8H-pyrido[2',3':4,5]pyrimido[6,1-b]quinazolin-8-one (4u). IR (KBr) ν_{max} : 1712 (C=O), 1608 (C=N) cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3 , δ in ppm) 2.43 (s, 3H, CH₃), 7.18-8.78 (m, 13H Ar-H), $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz, δ in ppm) 21.3, 116.3, 119.7, 121.7, 123, 123.3, 123.3, 124.6, 128.8, 128.8, 129.3, 129.3, 129.5, 129.5, 130.3, 132.3, 134.8, 136, 136.3, 139, 143.5, 148.5, 148.6, 155.9, 157.7, 163, 170.6; m/z (EI): 528.02 (25%); Anal. calcd for $\text{C}_{27}\text{H}_{16}\text{BrClN}_4\text{O}$: C, 61.44; H, 3.06; N, 10.62%. Found: C, 61.28; H, 3.24; N, 10.87%.

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